REMARKS

Claims 10, 13-15, and 39-73 are pending, claims 51-71 having been canceled by this amendment. Independent claims 10 and 43 have been amended to more clearly define the target cell and to clarify the length limitation, as suggested by the examiner; the amendment is supported by the specification at page 3, lines 23-29; page 4, lines 12-14; and page 14, lines 13-15. New claims 72 and 73, which require antisense nucleic acids 10-20 nucleotides in length, were added; the new claims are supported by disclosure at page 4, lines 13-14.

With respect to the Declaration/Power of Attorney, co-inventor, Dr. Carlson, has initialed and dated the correction of his home address. An initialed/dated copy of the Combined Declaration and Power of Attorney document is submitted herewith.

No new matter has been added by this amendment.

35 U.S.C. §112, first paragraph

Claims 10, 13-15, and 39-71 were rejected for failure to comply the requirements of §112.

Support for amended claims - new matter

With regard to new matter, the Examiner states in the paragraph spanning pages 2-3 of the Office Action:

> The instant claims 10, 43, 51 and 59 have been amended to recite the limitation "said nucleic acid comprising 10-50 nucleotides in length". New claim 69 has been added which also carries this limitation. The specification as filed states "Preferably the length is between 10-50 nucleotides, inclusive" (page 4, lines 13-14). This is not adequate support for the limitation of "comprising" 10-50 nucleotides as the term "inclusive" limits the fragments to fragments consisting of 10-50 nucleotides.

Claims 51-59 have been canceled, and claims 10 and 43 have been amended to address the Examiner's comments to require that the nucleic acid consist of between 10-50 nucleotides, inclusive. Withdrawal of this ground for rejection is therefore requested.

Written Description

With regard to written description, the Examiner states (on page 3, lines 19-25 of the Office Action):

> the term AAH reads on any asparyl asparaginyl beta-hydroxylase, and is not limited to human aspartyl asparaginyl beta-hydroxylase. The claims are thus dependent upon a genus of AAH antisense nucleic acids. With respect to HAAH protein, the instant specification provides a written description of the protein of SEQ ID NO:2 encoded by the cDNA of SEQ ID NO:3. When given the broadest reasonable interpretation, the claims drawn to AAH also embody, in addition to AAH from any species, allelic and splice variants, as well as any 5' regulatory regions and signal peptides.

The claims have now been amended to require that the antisense nucleic acids are complementary to a human AAH sequence. Specifically, the claims now require that the antisense nucleic acids are complementary to a 5' regulatory region of SEQ ID NO:3 or a 5' coding region of SEQ ID NO:3, provided that the coding region contains the initiating ATG methionione-encoding codon. In view of this amendment to recite a specific SEQ ID NO, Applicants submit that the written description requirement has been met.

The Examiner further states (page 5, lines 8-18):

> the instant specification may provide an adequate written description of the nucleic acids antisense to the 5' regulatory region of AAH, signal peptide, exon-1 or the coding sequence, per Lilly by structurally describing a representative number of species representative of each genus, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus"
>
> In this case, the specification does not describe any AAH 5' regulatory region, in a manner that satisfies the Lilly standards. The specification describes the coding regions of HAAH, and exon 1 of HAAH is known in the art. Although the specification discloses

> a single member of the AAH coding sequence, this does not provide a description of the genus of AAH coding sequences or EXON-1s that would satisfy the written description requirement by the standards set out in Lilly.

As is discussed above, the claims have been amended to require the nucleotide sequence of a single species, HAAH (SEQ ID NO:3). With regard to 5' regulatory region, claim 10 now requires the 5' regulatory region of SEQ ID NO:3, i.e., the eleven nucleotides of SEQ ID NO:3 that precede the ATG initiation codon. With respect to the coding region, claim 43 has been amended to require the portion of the coding region of SEQ ID NO:3 that includes the initiating ATG codon. In view of these amendments, Applicants submit that the requirements of the written description requirement as set out by the Patent Office and interpreted by the Lilly court have been met.

Enablement

Claims 10, 13-15, and 39-71 were rejected for failure to fulfill the enablement requirement. Claims 51-71 have been canceled, and independent claim 10 and 43 have been amended to require specific portions of SEQ ID NO:3. Claim 10 now requires a sequence that is complementary to the 5' regulatory region of SEQ ID NO:3, and claim 43 requires a sequence that is complementary to a coding region of SEQ ID NO:3 containing the initiating ATG codon. Both independent claims require that the length of the antisense nucleic acid consist of a length of 10-50 nucleotides.

In support of the rejection, the Examiner states:

> Broadus et al. [Methods in Enzymology, 2000, Vol. 314, pp. 121-135] teaches that a highly empirical approach to the testing of candidate antisense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification,

therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

In view of the present claim amendments, Applicants submit the amount of experimentation that would be required to determine whether an antisense construct encompassed by the claims inhibits tumor growth is not undue. For example, claim 10 requires that the nucleic acid be 10-50 nucleotides in length and contain a sequence that is complementary to a 5' regulatory sequence of SEQ ID NO:3. The 5' regulatory portion of SEQ ID NO:3 is a sequence of 11 nucleotides just 5' to the underlined ATG initiating codon (see Table 2 of the specification). Thus, 50 or fewer nucleic acids/oligonucleotides would have to be tested. Claim 43 now requires complementarity to a coding region of SEQ ID NO:3 and also requires that the 10-50 nucleotide antisense nucleic acid overlap the ATG initiating codon of SEQ ID NO:3. The claimed antisense constructs correspond to a relatively small region of SEQ ID NO:3; the entire target sequence is less than 60 nucleotides in length (see portion of SEQ ID NO:3 reproduced below). Although claim 43 encompasses a greater number of constructs, the amount of experimentation is by no means undue given the short and clearly delineated region of SEQ ID NO:3 defined by the amended claims.

Moreover, three representative antisense constructs in the relevant region of SEQ ID NO:3 have already been tested both *in vitro* and *in vivo*. As described in the accompanying Declaration of Jack R. Wands, animal studies were carried out to determine the effect of AAH antisense nucleic acids on tumors using an art-recognized rat model for cancer. The sequence of tested AAH antisense oligonucleotides was complementary to the sequence SEQ ID NO:3 (page 7 of the specification of the above-referenced patent application) and overlapped the initiation

codon of the human AAH mRNA, starting at –1, -6, and –11 relative to the ATG initiating methionine-encoding codon of human AAH sequence, as shown below.

```
5'CGGACCGTGC AATGGCCCAG CGTAAGAATG CCAAGAGCAG CGGCAACAGC AGCAGCAGCG  (SEQ ID NO:3)

3'GCCTGGCACG TTACCGGGTC GCATTCTTAC GGTTCACGTC GCCGTTGTCG TCGTCGTCGC 5'(COMPLEMENT)

            TTACCGGGTC GCATTCTTAC 5'  (AAH antisense -1)
     GGCACG TTACCGGGTC GCATTCTT   5'  (AAH antisense -6)
  GCCTGGCACG TTACCGGGTC           5'  (AAH antisense -11)
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The results of the study indicated that AAH antisense oligonucleotides defined by the amended claims reduced AAH gene expression and inhibited tumor growth/progression *in vivo*. Given the scope of the amended claims and the data indicating that three representative antisense nucleic acids in the defined area of SEQ ID NO:3 work as predicted by the specification, one of skill in the art would have more than a reasonable expectation of success that other antisense constructs within the defined parameters of the amended claims would have the same anti-tumor activity.

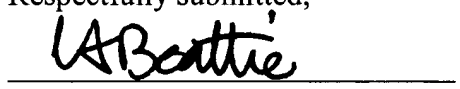
The nature and amount of experimentation required to practice the invention as now claimed is routine rather than excessive or undue, and the demonstration of success with exemplary antisense nucleic acids in the region of SEQ ID NO:3 confirms and verifies the teachings of the specification regarding tumor inhibition. Therefore, Applicants request withdrawal of this rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance.

Applicants file concurrently herewith a petition for a two (3) month extension of time, together with a check for $490.00 to cover the fee pursuant to 37 C.F.R. § 1.17(a)(3). With the extension, this amendment is due on or before November 22, 2004. The Commissioner is hereby authorized to charge same, or credit any overpayment, to Deposit Account No. 50-0311 (Reference No. 21486-032).

Respectfully submitted,



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